NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

AZT

(CAS NO. 30516-87-1)

AND

AZT/α-INTERFERON A/D

IN B6C3F$_1$ MICE

(GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

February 1999

NTP TR 469

NIH Publication No. 99-3959

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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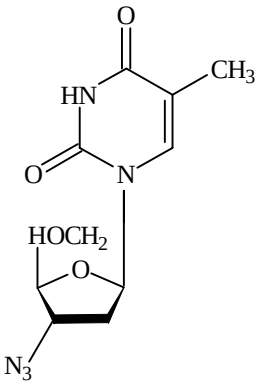
CONTENTS

ABSTRACT



3′-AZIDO-3′-DEOXYTHYMIDINE

CAS No. 30516-87-1

Chemical Formula: $C_{10}H_{13}N_5O_4$ Molecular Weight: 267.24

Synonyms: AZT; 3′-azido-2′,3′-dideoxythymidine; azidodeoxythymidine; azidothymidine; 3′-azidothymidine; 3′-deoxy-3′-azidothymidine; 3′-deoxy-(8CI) (9CI); BW A509U; Compound S; ZDV; zidovudine
Trade name: Retrovir®

3′-Azido-3′-deoxythymidine (AZT) is the most widely used and evaluated chemotherapeutic agent for the treatment of persons with acquired immune deficiency syndrome (AIDS) and persons seropositive for human immunodeficiency virus (HIV). The National Cancer Institute nominated AZT for toxicity and carcinogenicity studies because of the impending large-scale use of AZT in the treatment of adult patients with AIDS or AIDS-related complex. α-Interferon A/D, which displays antiviral activity in mice, is a hybrid molecule composed of the N-terminal portion of human α-interferon A and the C-terminal portion of human α-interferon D. AZT and α-interferon A/D combination studies were conducted because *in vitro* studies of AZT and α-interferon have demonstrated that the combination is more effective in blocking HIV infection than either agent alone. Male and female B6C3F$_1$ mice received AZT (approximately 98% pure) in 0.5% aqueous methylcellulose by gavage for 14 weeks or 2 years. In addition, male and female B6C3F$_1$ mice received α-interferon A or α-interferon A/D by subcutaneous injection for 2 years, and male and female B6C3F$_1$ mice received AZT in 0.5% aqueous methylcellulose by gavage in combination with α-interferon A/D by subcutaneous injection for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, mouse bone marrow erythrocytes, and mouse peripheral blood erythrocytes.

14-WEEK AZT STUDY

Groups of 10 male and 10 female mice received AZT in 0.5% methylcellulose by gavage at doses of 0, 50, 100, 200, 800, or 2,000 mg/kg daily for 14 weeks. Additional groups of 10 male and 10 female mice received AZT in 0.5% methylcellulose by gavage at doses of 0, 100, 800, or 2,000 mg/kg daily for 14 weeks and then were held without treatment for an additional 4 weeks before necropsy. One female receiving 100 mg/kg and two females receiving

200 mg/kg died during week 1 as a result of gavage trauma; one female receiving 2,000 mg/kg also died prior to the end of the 14-week dosing period. One female receiving 2,000 mg/kg in the recovery study also died from gavage trauma during week 1. The final mean body weights of dosed mice were similar to those of the vehicle control groups at the end of the dosing period and at the end of the recovery period. Female mice receiving 200, 800, or 2,000 mg/kg gained less weight than the vehicle controls during the 14-week dosing period.

Exposure to AZT was toxic to the bone marrow, resulting in significant changes in the peripheral blood (decreased hematocrit values, erythrocyte counts, and hemoglobin concentrations, and increased mean cell volume and mean cell hemoglobin) and bone marrow (erythroid hypoplasia) characteristic of a dose- and time-dependent, minimal to moderate, poorly regenerative macrocytic anemia. At the end of the 4-week recovery period, the hematology parameters had returned to normal, indicating that the hematotoxicity was reversible.

2-YEAR STUDIES

AZT

Groups of 95 male and 95 female mice received AZT in 0.5% methylcellulose by gavage at daily doses of 0, 30, 60, or 120 mg/kg body weight, administered as two equal doses at least 6 hours apart, 5 days per week for 105 weeks. Each group of 95 animals was composed of a core group of 50 animals for evaluation of carcinogenic response, a group of 30 animals for evaluation of hematology and bone marrow cellularity, and a group of 15 animals from which blood was drawn for determination of plasma AZT concentrations at week 54.

α-Interferon A/D and AZT/α-Interferon A/D Studies

Groups of 80 male and 80 female mice received AZT in 0.5% aqueous methylcellulose by gavage at daily doses of 0, 30, 60, or 120 mg/kg body weight, given in two equal doses, 5 days per week for 105 weeks. Those groups receiving AZT also received subcutaneous injections of 500 or 5,000 U α-interferon A/D three times per week for 105 weeks. Additional groups of 80 male and 80 female mice received subcutaneous injections of the vehicle, 500 U α-interferon A/D, 5,000 U α-interferon A/D, or 5,000 U α-interferon A, three times per week for 105 weeks.

Each group of 80 animals was composed of a core group of 50 animals for evaluation of carcinogenic response and a group of 30 animals for evaluation of hematology and bone marrow cellularity.

Because of the large number of animals involved, the 2-year studies were started in four phases and, for clarity, are presented as follows: the AZT study, the α-interferon A/D study, the AZT/500 U α-interferon A/D study, and the AZT/5,000 U α-interferon A/D study.

Design of the 2-Year AZT, AZT/α-Interferon A/D, and α-Interferon A/D Studies

AZT Dose	AZT Study	AZT/500 U α-Interferon A/D Study	AZT/5,000 U α-Interferon A/D Study	500 or 5,000 U α-Interferon A/D or 5,000 U α-Interferon A Study
Vehicle Control	95 male and 95 female mice[a]	80 male and 80 female mice[b]	80 male and 80 female mice[b]	80 male and 80 female mice[b]
30 mg/kg AZT	95 male and 95 female mice	80 male and 80 female mice	80 male and 80 female mice	None
60 mg/kg AZT	95 male and 95 female mice	80 male and 80 female mice	80 male and 80 female mice	None
120 mg/kg AZT	95 male and 95 female mice	80 male and 80 female mice	80 male and 80 female mice	None

[a] For the AZT study, there were 95 male and 95 female mice; these were divided into 50 males and 50 females in the core groups, 30 males and 30 females in the clinical pathology groups (hematology and bone marrow analyses only), and 15 males and 15 females for plasma AZT concentration determinations.

[b] For the α-interferon A/D study and the AZT/α-interferon A/D studies, there were 80 male and 80 female mice for each study; these were divided into 50 males and 50 females in the core groups and 30 males and 30 females in the clinical pathology groups (hematology and bone marrow analyses only).

Survival and Body Weights

Survival and mean body weights of mice exposed to AZT, α-interferon A, α-interferon A/D, or AZT plus α-interferon A/D were generally similar to those of the vehicle control groups.

Hematology and Bone Marrow Analyses

All groups of male and female mice receiving AZT exhibited changes in peripheral blood and bone marrow characteristic of a dose- and time-dependent, minimal to mild, macrocytic, nonresponsive anemia. In females, these changes were evident throughout the study. In males, the macrocytic anemia had resolved by week 80 in the 30 mg/kg group; at study termination erythrocyte macrocytosis was present only in males receiving 60 or 120 mg/kg AZT or AZT plus α-interferon A/D. There were no treatment-related alterations in hematology or bone marrow parameters in groups that received only α-interferon A or A/D.

Pathology Findings

Incidences of squamous cell carcinoma and squamous cell papilloma or carcinoma (combined) of the vagina occurred with a positive trend and were significantly increased in groups of female mice receiving 60 or 120 mg/kg AZT alone or in combination with α-interferon A/D. Epithelial hyperplasia was observed in all dosed groups of females, and the incidence was significantly increased in the 120 mg/kg AZT group.

Three renal tubule adenomas and one renal tubule carcinoma were observed in male mice receiving 120 mg/kg AZT; the combined incidence in this group exceeded the range in historical controls. A renal tubule adenoma was observed in one male receiving 60 mg AZT/kg and 500 U α-interferon A/D; however, none were observed in other groups. Evaluation of step sections revealed a few more renal tubule hyperplasias but no additional neoplasms.

The incidence of harderian gland adenoma was increased in male mice receiving 120 mg/kg AZT and exceeded the range in historical controls. Harderian gland neoplasms were observed in other groups but did not follow a treatment-related pattern.

Overall Incidences of Vaginal Neoplasms and Hyperplasia of the Vaginal Epithelium in Female Mice in the 2-Year Gavage Studies of AZT and AZT/α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg	60 mg AZT/kg	120 mg AZT/kg
AZT alone	2/197 (1%)[b] 1/197	0/49 (0%) 3/49	5/45 (11%) 4/45	11/49 (22%) 11/49
500 U α-Interferon A/D	0/49 (0%) 0/49	0/44 (0%) 4/44	5/48 (10%) 8/48	6/48 (13%) 12/48
5,000 U α-Interferon A/D	1/50 (2%) 1/50	1/48 (2%) 4/48	5/48 (10%) 8/48	4/50 (8%) 15/50

[a] Data are presented as number of vaginal neoplasms/number of animals microscopically examined (first line) and number of vaginal hyperplasias/number of animals microscopically examined (second line)
[b] Combined incidences of controls from the AZT alone study and the AZT/α-interferon A/D studies; incidences in the vehicle control group from the AZT alone study are 0/50 (0%) (neoplasms) and 0/50 (hyperplasia)

Overall Incidence of Harderian Gland Neoplasms in Male Mice in the 2-Year Gavage Studies of AZT and AZT/α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg	60 mg AZT/kg	120 mg AZT/kg
AZT alone	13/200 (6%)[b]	5/50 (10%)	2/50 (4%)	10/50 (20%)
500 U α-Interferon A/D	3/50 (6%)	3/50 (6%)	1/50 (2%)	4/50 (8%)
5,000 U α-Interferon A/D	3/50 (6%)	9/50 (18%)	4/50 (8%)	4/50 (8%)

[a] Data are presented as number of harderian gland neoplasms/number of animals necropsied
[b] Combined incidences of controls from the AZT alone study and the AZT/α-interferon A/D studies; incidence in the vehicle control group from the AZT alone study is 3/50 (6%)

Male mice had a pattern of nonneoplastic liver lesions along with silver-staining helical organisms within the liver consistent with an infection with *Helicobacter hepaticus*. An organism compatible with *H. hepaticus* was confirmed by polymerase chain reaction-restriction fragment length polymorphism-based assays. Detection of dose-related differences in neoplasm incidences in these studies was not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis.

GENETIC TOXICOLOGY

AZT is mutagenic *in vitro* and *in vivo*. It induced gene mutations in *Salmonella typhimurium* strain TA102, with and without S9; no increases in mutations were noted in the other tested strains of *S. typhimurium*. AZT induced sister chromatid exchanges, but not chromosomal aberrations, in cultured Chinese hamster ovary cells, with and without S9. *In vivo* studies with male mice administered AZT by gavage showed highly significant increases in micronucleated erythrocytes in bone marrow and peripheral blood after exposure periods that ranged from 72 hours to 14 weeks.

CONCLUSIONS

Under the conditions of these 2-year gavage studies there was *equivocal evidence of carcinogenic activity** of AZT in male mice based on increased incidences of renal tubule and harderian gland neoplasms in groups

receiving AZT alone. There was *clear evidence of carcinogenic activity* of AZT in female mice based on increased incidences of squamous cell neoplasms of the vagina in groups that received AZT alone or in combination with α-interferon A/D.

Hematotoxicity occurred in all groups that received AZT.

Treatment with AZT alone and AZT in combination with α-interferon A/D resulted in increased incidences of epithelial hyperplasia of the vagina in all dosed groups of females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 14. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 16.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of AZT and AZT/α-Interferon A/D in Mice

	AZT	α-Interferon A/D	AZT/500 U α-Interferon A/D	AZT/5,000 U α-Interferon A/D
Doses	0, 30, 60, or 120 mg AZT/kg body weight in 0.5% methylcellulose by gavage, given 5 days per week in two equal doses of 0, 15, 30, or 60 mg/kg per dose	0, 500, or 5,000 U α-interferon A/D or 5000 U α-interferon A administered subcutaneously three times per week	0, 30, 60, or 120 mg AZT/kg body weight in 0.5% methylcellulose by gavage, given 5 days per week in two equal doses of 0, 15, 30, or 60 mg/kg per dose. Dosed groups also received 500 U α-interferon A/D administered subcutaneously three times per week.	0, 30, 60, or 120 mg AZT/kg body weight in 0.5% methylcellulose by gavage, given 5 days per week in two equal doses of 0, 15, 30, or 60 mg/kg per dose. Dosed groups also received 5,000 U α-interferon A/D administered subcutaneously three times per week.
Body weights	Dosed groups similar to vehicle control groups	Dosed groups generally similar to vehicle control groups	Dosed groups similar to vehicle control groups	Dosed groups similar to vehicle control groups
2-Year survival rates	Males 32/50, 35/50, 29/50, 42/50 Females 34/50, 39/50, 31/50, 31/50	Males 27/50, 28/50, 28/50 Females 25/50, 32/50, 25/50	Males 36/50, 27/50, 38/50, 35/50 Females 33/50, 32/50, 32/50, 24/49	Males 31/50, 35/50, 35/50, 34/50 Females 37/50, 38/50, 36/50, 32/50
Nonneoplastic effects	Females Vagina: epithelial hyperplasia (0/50, 3/49, 2/45, 7/49); atypical hyperplasia (0/50, 0/49, 2/45, 4/49)	None	Females Vagina: epithelial hyperplasia (0/49, 4/44, 6/48, 11/48); atypical hyperplasia (0/49, 0/44, 2/48, 1/48)	Females Vagina: epithelial hyperplasia (1/50, 3/48, 7/48, 12/50); atypical hyperplasia (0/50, 1/48, 1/48, 3/50)
Neoplastic effects	Females Vagina: squamous cell carcinoma (0/50, 0/49, 5/45, 9/49); squamous cell papilloma or carcinoma (0/50, 0/49, 5/45, 11/49)	None	Females Vagina: squamous cell carcinoma (0/49, 0/44, 5/48, 6/48)	Females Vagina: squamous cell carcinoma (0/50, 0/48, 5/48, 4/50)
Uncertain findings	Males Kidney: renal tubule adenoma (0/50, 0/48, 0/49, 3/50); renal tubule carcinoma (0/50, 0/48, 0/49, 1/50) Harderian gland: adenoma (3/50, 2/50, 2/50, 10/50); adenoma or carcinoma (3/50, 5/50, 2/50, 10/50)	None	None	None

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of AZT and AZT/α-Interferon A/D in Mice

		AZT	α-Interferon A/D	AZT/500 U α-Interferon A/D	AZT/5,000 U α-Interferon A/D
Level of evidence of carcinogenic activity	Males	Equivocal evidence			
	Females	Clear evidence			
Genetic toxicology					
Salmonella typhimurium gene mutations:		Positive in strain TA102 with and without S9; negative in strains TA97, TA98, TA100, TA104, and TA1535, with and without S9			
Sister chromatid exchanges					
Cultured Chinese hamster ovary cells *in vitro*:		Positive with and without S9			
Chromosomal aberrations					
Cultured Chinese hamster ovary cells *in vitro*:		Negative with and without S9			
Micronucleated erythrocytes					
Mouse bone marrow *in vivo*:		Positive			
Mouse peripheral blood *in vivo*:		Positive			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

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TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on AZT and AZT/α-interferon A/D on 11 December 1996 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 11 December 1996, the draft Technical Report on the toxicology and carcinogenesis studies of 3′-azido-3′-deoxythymidine (AZT) and AZT/α-interferon A/D received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of AZT and AZT/α-interferon A/D by discussing the uses of the chemicals and rationale for study, describing the experimental design (including a recovery group of mice to assess reversibility of bone marrow changes), reporting on the lack of survival and body weight effects, and commenting on treatment-related neoplasms and nonneoplastic lesions in mice. The proposed conclusions for the 2-year studies in mice were *equivocal evidence of carcinogenic activity* of AZT in male mice and *clear evidence of carcinogenic activity* of AZT in female mice.

Dr. LeBoeuf, a principal reviewer, agreed with the proposed conclusions. He noted the presence of *Helicobacter hepaticus* as a potential confounding factor for interpretation of liver lesions, but agreed that in this case it would not have an impact on the level of evidence for males or females.

Dr. Reddy, the second principal reviewer, agreed with the proposed conclusions. He asked why the studies were not also conducted in rats and whether there were any case reports indicating an increase in vaginal neoplasms in human females. Dr. Irwin responded that Burroughs Wellcome had conducted asatisfactory study in rats. Dr. K.M. Ayers, Glaxo Wellcome, reported that the findings have been cited in the *Physicians Desk Reference* since about 1990. Dr. Irwin said there are no reports in the literature of genital neoplasms associated with the use of AZT in human females. Dr. Reddy said that, nonetheless, the findings could raise concerns because of the genital papillomas and warts reported in human papilloma virus infected HIV-positive men and women.

Dr. Tyson, the third principal reviewer, agreed with the proposed conclusions. He asked about the rationale for the strain of mice used and thought it would have been of interest to have used a strain of immunocompromised mice. Dr. Tyson commented that useful insights might have been gained from looking for molecular markers found in human vaginal tumors, such as activated oncogenes or certain papilloma viruses. Dr. Irwin said that with the complexity of the study, it was preferred to use the $B6C3F_1$ model for which there was a large historical database.

Dr. Goldsworthy asked whether higher incidences of hepatoblastoma in mice might be associated with *H. hepaticus*. Dr. J.R. Hailey, NIEHS, said that NTP had seen hepatoblastomas more frequently in recent studies as part of what seems to be a progression of that lesion.

Dr. LeBoeuf moved that the Technical Report on AZT and AZT/α-interferon A/D be accepted with the revisions discussed and the conclusions as written for male mice, *equivocal evidence of carcinogenic activity*, and for female mice, *clear evidence of carcinogenic activity*. Dr. Reddy seconded the motion, which was accepted unanimously with eight votes.